



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: July 6, 2011

To: M. Dianne Murphy, MD  
Director, Office of Pediatric Therapeutics (OPT), OIASI  
Office of the Commissioner

CDR Lisa L. Mathis, USPHS, MD  
Director, Pediatric and Maternal Health Team  
Office of New Drugs

Through: Laura Governale, Pharm.D., MBA  
Drug Use Data Analyst Team Leader  
Division of Epidemiology II  
Office of Surveillance and Epidemiology

Hina Mehta, Pharm.D.  
Drug Use Data Analyst Team Leader  
Division of Epidemiology II  
Office of Surveillance and Epidemiology

From: Grace Chai, Pharm.D.  
Drug Use Data Analyst  
Division of Epidemiology II  
Office of Surveillance and Epidemiology

Subject: Topiramate BPCA Drug Use Review

Drug Name(s): Topiramate (Topamax® and Topamax Sprinkles®)

Application Type/Number: NDA 20-505, 20-844

Applicant/sponsor: Ortho McNeil Janssen

OSE RCM #: 2011-1218

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## EXECUTIVE SUMMARY

This review examines drug utilization patterns in the pediatric population (patients aged 0-1, 2-9, and 10-16 years) for topiramate (Topamax<sup>®</sup> and Topamax Sprinkles<sup>®</sup>).

Approximately 82% of the topiramate market was sold to U.S. outpatient retail settings during the 12-month period ending in March 2011. Therefore, this review focuses on the outpatient retail setting.

For the four 12-month periods from April 2007 through March 2011:

- Topiramate was the fifth most frequently dispensed medication out of the prescriptions dispensed for seizure disorder medications (USC class 20200) to the pediatric population (0-16 years) during the 12-month period ending March 2011.
- Approximately 32.7 million prescriptions were dispensed and 4.35 million patients received dispensed prescriptions for topiramate from outpatient retail pharmacies from April 2007 through March 2011, cumulative.
  - Prescriptions dispensed to the pediatric population (ages 0-16) accounted for approximately 2.1 million prescriptions (6.5% of prescriptions) and 315,000 patients (7% of patients).
- Topiramate prescriptions dispensed to the total population increased 19% from the 12-month period ending in March 2008 to the 12-month period ending in March 2011, while prescriptions dispensed to the pediatric population remained relatively steady.
- Neurologists were the top prescribing specialty (31% of prescriptions), while Pediatricians accounted for nearly 2% of topiramate prescriptions during the examined time.
- Top diagnoses associated with topiramate use in younger pediatric patients (0-9 years) were for epilepsy and convulsions diagnoses, while the top diagnoses in older pediatric patients (10-16 years) and in adults were for migraine and headache diagnoses.

## 1 BACKGROUND

### 1.1 INTRODUCTION

The Office of Pediatric Therapeutics (OPT) and Pediatric and Maternal Health Staff (PMHS) requested a review of the drug utilization patterns for topiramate (Topamax<sup>®</sup> and Topamax Sprinkles<sup>®</sup>) in preparation for the Pediatric Advisory Committee meeting to be held in September 2011. Using the currently available proprietary drug use databases licensed by the Agency, this review provides the outpatient retail drug use patterns for Topamax<sup>®</sup> (topiramate), with a focus on the pediatric population (0-16 years), for four 12-month periods from April 2007 through March 2011.

## 1.2 REGULATORY HISTORY

Topamax<sup>®</sup> (topiramate) was initially approved for marketing in December 1996. Pediatric exclusivity was granted on July 24, 2008. Pediatric trials that were conducted suggested some adverse reactions/toxicities not previously observed in older pediatric patients and adults (e.g., growth retardation, lab abnormalities and higher frequency of metabolic acidosis). A Medication Guide REMS (Risk Evaluation and Mitigation Strategy) was approved on April 23, 2009, and modified on March 4, 2011, informing patients of the serious risks associated with topiramate, including suicidal thoughts and behavior.

## 1.3 PRODUCT LABELING

Topamax<sup>®</sup> (topiramate) is an antiepileptic (AED) agent indicated for:

- Monotherapy epilepsy: Initial monotherapy in patients  $\geq 10$  years of age with partial onset or primary generalized tonic-clonic seizures.
- Adjunctive therapy epilepsy: Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures, and in patients  $\geq 2$  years of age with seizures associated with Lennox-Gastaut syndrome (LGS)
- Migraine: Treatment for adults for prophylaxis of migraine headache

Topamax<sup>®</sup> is available in 25 mg, 50 mg, 100 mg, and 200 mg oral tablets and as sprinkle capsules in 15 mg and 25 mg strengths.<sup>1</sup>

## 2 METHODS AND MATERIALS

### 2.1 DETERMINING SETTINGS OF CARE

IMS Health, IMS National Sales Perspectives<sup>™</sup> data (see *Appendix 2* for full database description) was used to determine the settings in which topiramate products were sold. Sales data for the 12-month period ending in March 2011 indicated that approximately 82% of topiramate bottles and packages (eaches) were distributed to outpatient retail pharmacies, 12% to non-retail settings, and 6% to mail order pharmacies.<sup>2</sup> As a result, outpatient retail pharmacy utilization patterns were examined. Neither mail-order nor non-retail settings data were included in this analysis.

### 2.2 DATA SOURCES USED

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

Outpatient use and patient demographics (stratified by age 0-1 year, 2-9 years, 10-16 years, 17+ years) were measured from SDI, Vector One<sup>®</sup>: National (VONA) and Total Patient Tracker (TPT) (*Appendix 2*). Indications for use were obtained from the SDI's Physician Drug and

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<sup>1</sup> Topamax<sup>®</sup> (topiramate) product label, Ortho-McNeil Janssen Pharmaceuticals, Inc. Revised December 2009. Accessed June 2011.

<sup>2</sup> IMS Health, IMS National Sales Perspectives<sup>™</sup>. April 2010 – March 2011. Data extracted June 2011, Source file: 1106topi.xls.

Diagnosis Audit (PDDA) (*Appendix 2*). From these data sources, estimates of the number of prescriptions dispensed, the number of patients who received a prescription for topiramate products, and the number of drug mentions by office-based physicians, were obtained for the four 12-month periods from April 2007 through March 2011.

### **3 RESULTS**

#### **3.1 TOPIRAMATE AND COMPARATOR DRUGS PRESCRIPTION DATA**

Figure 1 in Appendix 1 shows the projected number of dispensed prescriptions for the top medications in the seizure disorders class (USC class 20200) for pediatric patients (0-16 years) from U.S. outpatient retail pharmacies by 12-month periods from April 2007 through March 2011. Throughout the time period studied, divalproex was the most commonly dispensed agent among patients aged 0-16 years. Topiramate was the fifth most frequently dispensed medication out of the seizure disorder medications dispensed to the pediatric population during the 12-month period ending March 2011.

#### **3.2 TOPIRAMATE PRESCRIPTION DATA**

Table 1 in Appendix 1 shows the projected number of topiramate prescriptions by patient age dispensed from U.S. outpatient retail pharmacies during April 2007 through March 2011. Approximately 32.7 million topiramate prescriptions were dispensed during the examined time. Pediatric patients aged 0-16 years accounted for 6.5% of the total (2.1 million prescriptions) prescriptions dispensed from April 2007 through March 2011, cumulative. Of the prescriptions dispensed to pediatric patients, the majority were for patients aged 10-16 years with 73% of the pediatric prescriptions (1.5 million prescriptions) followed by patients aged 2-9 years and 0-1 year, with 25% (523,000 prescriptions) and 2% of prescriptions (47,800 prescriptions), respectively, during the examined time.

Topiramate prescriptions dispensed to the total population increased by 19% from 7.5 million prescriptions in the 12-month period ending in March 2008 to 8.9 million prescriptions in the 12-month period ending in March 2011. Prescriptions for the pediatric population aged 0-16 years remained relatively steady during the examined time with approximately 529,000 prescriptions dispensed in the 12-month period ending March 2011.

#### **3.3 TOPIRAMATE PATIENT DATA**

Table 2 in Appendix 1 shows the projected number of patients who received dispensed prescriptions for topiramate, stratified by age, from U.S. outpatient retail pharmacies, April 2007 through March 2011. Approximately 4.35 million patients received prescriptions for topiramate during the examined time. Pediatric patients aged 0-16 years accounted for 7% of the total (315,000 patients) during the examined time. Of the pediatric patients receiving dispensed prescriptions for topiramate, the majority were aged 10-16 years, accounting for 81% of pediatric patients (255,000 patients), followed by patients aged 2-9 years and 0-1 year, accounting for 21% (65,600 patients) and 3% (8,900 patients) of patients, respectively.

In general, patient count data followed similar trends as prescription count data. Patients receiving topiramate prescriptions increased 14% from 1.7 million patients in the 12-month period ending in March 2008 to 1.9 million patients in the 12-month period ending in March 2011. The number of pediatric patients aged 0-16 years receiving topiramate prescriptions

remained relatively steady during the examined time with about 119,000 pediatric patients during the 12-month period ending March 2011.

### **3.4 PRESCRIBING SPECIALTIES**

Table 3 in Appendix 1 shows the top prescribing specialties for topiramate by the projected number of prescriptions dispensed from U.S. outpatient retail pharmacies from April 2007 through March 2011, cumulative. Neurologists were the top prescribing specialty accounting for approximately 31% (10.1 million prescriptions) of topiramate prescriptions dispensed during the examined time. “General Practice/Family Medicine/Doctors of Osteopathy” accounted for 20% (6.6 million prescriptions) of prescriptions, and “Psychiatry” accounted for 13% (4.3 million prescriptions) of prescriptions during the examined time. Pediatricians accounted for approximately 2% (540,000 prescriptions) of topiramate prescriptions dispensed during April 2007 through March 2011, cumulative.

### **3.5 DIAGNOSES DATA**

Table 4 in Appendix 1 shows the top diagnoses (ICD-9 codes) by the projected number of use mentions for topiramate by patient age (0-1 year, 2-9 years, 10-16 years, and 17+ years) as reported by U.S. office-based physician survey for April 2007 through March 2011, cumulative. Diagnoses associated with epilepsy or convulsions (ICD-9 codes 345.9, 345.5, 345.1, and 780.3) were the top diagnoses in the younger pediatric patients aged 0-1 year and 2-9 years with 69% and 59% of topiramate uses, respectively. Migraines and headache diagnoses (ICD-9 codes 346.9, 346.0, and 784.0) were the top diagnoses in the older pediatric population (10-16 years), as well as in the adult population with slightly greater than half of topiramate uses during the examined time.

## **4 DISCUSSION**

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that topiramate products were distributed primarily to the outpatient settings based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use. The estimates from our analysis therefore only apply to the outpatient retail setting and not necessarily to other settings of care.

Pediatric utilization accounted for about 6-7% of outpatient topiramate use during the examined time. Although adult use of topiramate slightly increased, pediatric utilization of topiramate products appears relatively steady during the examined time.

Diagnoses associated with epilepsy or convulsions were the top diagnoses in the younger pediatric patients (0-1 year and 2-9 years). However, in pediatric patients aged 10-16 years and in adults, migraine and headache diagnoses accounted for the largest proportions of topiramate use during the examined time. It is important to note that although the use of topiramate for epilepsy is indicated in patients 2 years and older, the use for migraines is only indicated in adults.

SDI's Physician Drug & Diagnosis Audit (PDDA) data provide estimates of patient demographics and indications for use of medicinal products in the U.S. However due to the sampling and data collection methodologies, the small sample size can make these data unstable, particularly if use is not common in the pediatric population. SDI recommends caution interpreting projected annual uses or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals.

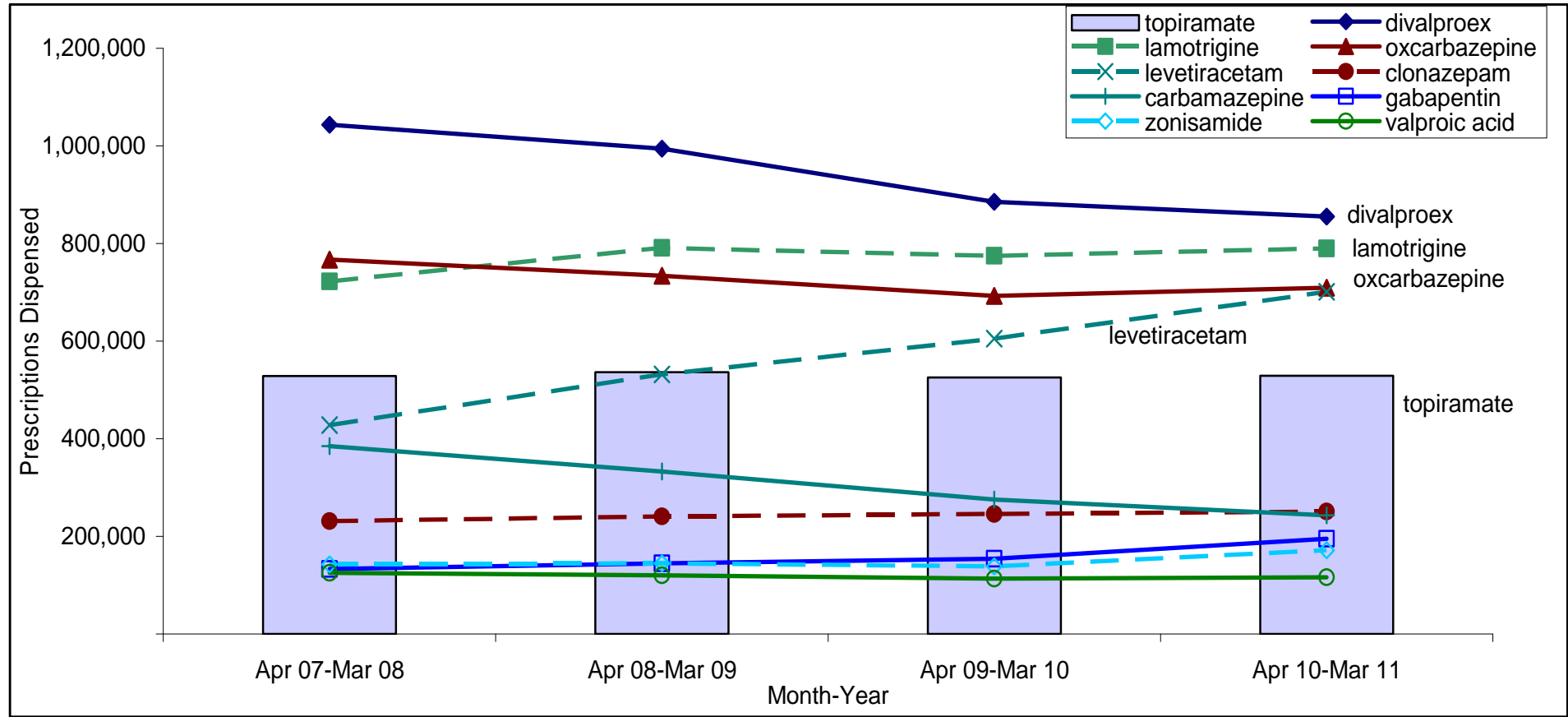
No statistical tests were performed to determine statistically significant changes over time or between products. It is important to note the small sample of these products when looking at the pediatric populations. Therefore, all changes over time or between products should be considered approximate and may be due to random error.

## **5 CONCLUSION**

Pediatric utilization accounted for about 6-7% of outpatient topiramate use during the examined time. Although the adult use of topiramate increased slightly, pediatric utilization of topiramate appears relatively steady during the examined time. The top diagnoses associated with topiramate use in younger pediatric patients (0-9 years) were for epilepsy and convulsions diagnoses, while the top diagnoses in older pediatric patients (10-16 years) and in adults were for migraine and headache diagnoses. However, these results must be interpreted with caution as the sample size was very small with correspondingly large confidence intervals.

APPENDIX 1: TABLES AND FIGURES

Figure 1:  
Projected number of prescriptions for the top 10 seizure disorder medications (USC class 20200)  
dispensed to the pediatric population (0-16 years) from U.S. retail pharmacies, April 2007 - March 2011



Source: SDI: Vector One®: National, Apr2007-Mar2011, Extracted June 2011. File: VONA 2011-1218 seizure disorders class 20200.xls

Table 1:

**Projected number of topiramate prescriptions by patient age dispensed from U.S. retail pharmacies,  
April 2007 - March 2011**

	Apr 07-Mar 08		Apr 08-Mar 09		Apr 09-Mar 10		Apr 10-Mar 11		Apr 2007 - Mar 2011	
	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%
<b>Topiramate Market</b>	7,510,050	100.0%	7,906,152	100.0%	8,409,692	100.0%	8,904,737	100.0%	32,730,631	100.0%
<b>0-16 years</b>	528,528	7.0%	536,297	6.8%	525,435	6.2%	529,142	5.9%	2,119,401	6.5%
<b>0-1 year</b>	12,069	2.3%	13,423	2.5%	11,703	2.2%	10,582	2.0%	47,777	2.3%
<b>2-9 years</b>	137,866	26.1%	134,215	25.0%	126,118	24.0%	124,525	23.5%	522,723	24.7%
<b>10-16 years</b>	378,593	71.6%	388,658	72.5%	387,614	73.8%	394,035	74.5%	1,548,900	73.1%
<b>17+ years</b>	6,981,506	93.0%	7,369,840	93.2%	7,884,216	93.8%	8,375,574	94.1%	30,611,136	93.5%
<b>Unspecified Age</b>	17	0.0%	15	0.0%	40	0.0%	22	0.0%	94	0.0%

Source: SDI: Vector One®: National, Apr2007-Mar2011, Extracted June 2011. Files: VONA 2011-1218 topiramate TRx 0-16.xls and VONA 2011-1218 topiramate TRx age.xls

Table 2:

**Projected number of unique patients by patient age receiving topiramate from outpatient retail settings,  
April 2007 - March 2011**

	Apr 07-Mar 08		Apr 08-Mar 09		Apr 09-Mar 10		Apr 10-Mar 11		Apr 2007 - Mar 2011	
	Patients	Share%	Patients	Share%	Patients	Share%	Patients	Share%	Patients	Share%
<b>Topiramate Market</b>	1,664,388	100.0%	1,651,385	100.0%	1,732,173	100.0%	1,891,311	100.0%	4,349,810	100.0%
<b>0-16 years</b>	117,142	7.0%	114,595	6.9%	114,236	6.6%	119,208	6.3%	315,378	7.3%
<b>0-1 year</b>	3,012	2.6%	3,086	2.7%	2,841	2.5%	2,604	2.2%	8,918	2.8%
<b>2-9 years</b>	27,077	23.1%	25,087	21.9%	23,835	20.9%	24,020	20.2%	65,587	20.8%
<b>10-16 years</b>	89,962	76.8%	89,152	77.8%	90,389	79.1%	95,341	80.0%	255,042	80.9%
<b>17+ years</b>	1,553,365	93.3%	1,543,373	93.5%	1,624,536	93.8%	1,778,771	94.0%	4,069,797	93.6%
<b>Unspecified Age</b>	10	0.0%	10	0.0%	15	0.0%	16	0.0%	51	0.0%

Source: SDI Vector One®: National and Total Patient Tracker (TPT). March 2006-February 2011. Extracted 04/11. Files: TPT 2011-1218 topiramate pts by age years.xls, TPT 2011-1218 topiramate pts 0-16 total.xls, TPT 2011-1218 topiramate pts 0-16 years.xls, TPT 2011-1218 topiramate pts by age total.xls

Table 3:

**Top prescribing specialties for topiramate by number of prescriptions dispensed from U.S. outpatient retail pharmacies, April 2007 - March 2011, cumulative**

	<b>Apr 07 - Mar 11</b>	
	<b>TRxs</b>	<b>Share%</b>
<b>Total Market</b>	<b>32,740,224</b>	<b>100.0%</b>
Neurology	10,096,924	30.8%
GP/FM/DO	6,592,561	20.1%
Psychiatry	4,313,776	13.2%
Internal Medicine	3,624,435	11.1%
Unspecified	2,010,885	6.1%
Nurse Practitioner	1,665,966	5.1%
Physician Assistant	746,453	2.3%
Other	668,709	2.0%
Anesthesiology	546,044	1.7%
<b>Pediatrics</b>	<b>539,577</b>	<b>1.6%</b>
<b>All Others</b>	<b>1,934,893</b>	<b>5.9%</b>

Source: SDI Vector One®: National, Apr07-Mar11. Data Extracted Jun11.

File: VONA 2011-1218 topiramate MD 06-2011.xls

GP/FM/DO – General Practice, Family Medicine, Doctor of Osteopathy

Table 4:

Top diagnoses associated with the projected number of use mentions for topiramate by patient age as reported by U.S. office-based physician survey, April 2007 - March 2011, cumulative

	Apr 07 - Mar 11	
	Uses (000)	Share%
<b>Topiramate Uses</b>	<b>9,118</b>	<b>100.0%</b>
0-1 year	19	0.2%
3459 EPILEPSY NOS	6	31.2%
3469 MIGRAINE NOS	6	30.9%
3455 PARTIAL EPILEPSY NEC	4	19.3%
7803 CONVULSIONS	4	18.7%
2-9 years	108	1.2%
3459 EPILEPSY NOS	31	28.7%
7803 CONVULSIONS	30	27.7%
2967 BIPOLAR AFFECTIVE NOS	9	8.5%
7840 HEADACHE	8	7.6%
3072 TICS	7	6.6%
V403 BEHAVIORAL PROBLEMS NEC	6	5.6%
2969 AFFECT PSYCHOSES NEC/NOS	5	4.7%
3140 ATTENTION DEFICIT DIS	4	4.1%
3469 MIGRAINE NOS	4	3.8%
3451 GEN CONVULSIVE EPILEPSY	3	2.7%
10-16 years	322	3.5%
3469 MIGRAINE NOS	107	33.3%
7840 HEADACHE	41	12.8%
2967 BIPOLAR AFFECTIVE NOS	29	9.0%
3459 EPILEPSY NOS	24	7.6%
7803 CONVULSIONS	24	7.4%
3140 ATTENTION DEFICIT DIS	23	7.1%
3460 CLASSICAL MIGRAINE	16	5.1%
2962 DEPR PSYCH, SINGL EPISOD	9	2.9%
2780 OBESITY	7	2.3%
3455 PARTIAL EPILEPSY NEC	7	2.1%
All Others	34	10.5%
17+ years	8,299	91.0%
3469 MIGRAINE NOS	3,910	47.1%
7840 HEADACHE	646	7.8%
7803 CONVULSIONS	533	6.4%
3459 EPILEPSY NOS	413	5.0%
2967 BIPOLAR AFFECTIVE NOS	347	4.2%
3455 PARTIAL EPILEPSY NEC	201	2.4%
3110 DEPRESSIVE DISORDER NEC	141	1.7%
3460 CLASSICAL MIGRAINE	102	1.2%
2962 DEPR PSYCH, SINGL EPISOD	94	1.1%
2957 SCHIZOAFFECTIVE TYPE	85	1.0%
All Others	1,827	22.0%
Unspecified Age	370	4.1%

Source: SDI Physician Drug & Diagnosis Audit (PDDA) with Pain Panel. Apr07-Mar11.

Extracted Jun2011. File: PDDA 2011-1218 topiramate ICD-9 by age.xls

## **APPENDIX 2: DATABASE DESCRIPTIONS**

### **IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail**

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

### **SDI's Vector One®: National (VONA)**

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.4 billion prescription claims per year, representing over 120 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing over 200 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

### **SDI's Vector One®: Total Patient Tracker (TPT)**

SDI's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.4 billion prescription claims per year, representing over 120 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing over 200 million unique patients.

### ***SDI Physician Drug & Diagnosis Audit (PDDA) with Pain Panel***

SDI's Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

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/s/  
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GRACE P CHAI  
07/15/2011

LAURA A GOVERNALE  
07/15/2011  
drug use data cleared